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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Burchard

Serial No.: 09/616,849 Art Unit: 1655

Filed: July 14, 2000 Examiner: Forman, B.

For: METHOD FOR DETERMINING THE SPECIFICITY AND SENSITIVITY OF OLIGONUCLEOTIDES FOR HYBRIDIZATION

Attorney Docket No: 9301-044

AMENDMENT UNDER 37 C.F.R. 1.111

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In response to the Office Action mailed November 5, 2001 in connection with the above-identified patent application and in accordance with Rule 111 of the Rules of Practice, please enter the following amendments and consider the following remarks. Applicant submits herewith: 1) Exhibit A: marked version of the paragraphs in the specification which have been amended; 2) Exhibit B: marked version of the amended claims showing changes made; 3) Exhibit C: clean version of the pending claims, as amended; and 4) Amendment Fee Transmittal (in duplicate), accompanied by the appropriate fee.

IN THE SPECIFICATION:

A marked version showing the amendment to the specification is attached hereto as Exhibit A.

Please amend the specification as follows:

Please delete page i, containing the Table of Contents.

IN THE CLAIMS:

A marked version of the claims showing the amendments is attached hereto as Exhibit B. Matter that has been deleted from claims 1, 4-13, 15, 20, 22-23, 25, 27-30, 33-40, 42-47,

55-59, 62, 67-72, 75 and 85 is indicated by brackets and matter that has been added is indicated by underlining. A clean version of the pending claims, as amended, is attached hereto as Exhibit C.

Please amend the claims as follows:

Please cancel claims 2, 3, 31, 32 and 41, without prejudice.

Please amend claims 1, 4-13, 15, 20, 22-23, 25, 27-30, 33-40, 42-47, 55-59, 62, 67-72, 75 and 85 to read as follows:

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1. (Amended) A method for evaluating binding properties of a probe to a target molecule, said method comprising comparing the amount of binding of molecules in a first sample to the probe with the amount of binding of molecules in a second sample to the probe, wherein:

(a) the first sample comprises a plurality of molecules of the target molecule; and

(b) the second sample comprises a plurality of different molecules,

wherein the first sample is at least 75% pure in said target molecule.

4. (Amended) The method of claim 1 wherein the first sample is at least 90% pure in said target molecule.

5. (Amended) The method of claim 4 wherein the first sample is at least 95% pure in said target molecule.

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6. (Amended) The method of claim 5 wherein the first sample is at least 99% pure in said target molecule.

7. (Amended) The method of claim 1 wherein each of said plurality of different molecules in the second sample is different from the target molecule in the first sample.

8. (Amended) The method of claim 1 wherein a sensitivity of the probe is determined, wherein said sensitivity is the absolute amount of molecules of said target molecule that bind to said probe.

9. (Amended) The method of claim 8 wherein the sensitivity of the probe is determined from the amount of binding of molecules of the target molecule in the first sample to the probe.

10. (Amended) The method of claim 1 wherein a specificity of the probe is determined, wherein said specificity is the amount of molecules of said target molecule that bind to said probe relative to the amount of other molecules that bind to said probe under the same binding conditions.

B2 cont

11. (Amended) The method of claim 10 wherein the specificity of the probe is determined from a ratio of the amount of binding to the probe of the molecules of the target molecule in the first sample to the amount of binding to the probe of molecules of the different molecules in the second sample.

12. (Amended) The method of claim 1 wherein the molecules of the target molecule in the first sample are detectably labeled.

13. (Amended) The method of claim 1 wherein the molecules of the plurality of different molecules in the second sample are detectably labeled.

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15. (Amended) The method of claim 1 wherein:

(a) the molecules of the target molecule in the first sample are detectably labeled with a first label; and

(b) the molecules of the plurality of different target molecules in the second sample are detectably labeled with a second label,

the first label being distinguishable from the second label.

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20. (Amended) The method of claim 1 wherein the probe is a polynucleotide probe comprising a predetermined nucleotide sequence.

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22. (Amended) The method of claim 21 wherein the predetermined nucleotide

sequence of the polynucleotide probe is complementary to at least a hybridizable portion of the nucleotide sequence of the polynucleotide molecules in the first sample.

B5 cont

23. (Amended) The method of claim 21 wherein the molecules of the different target molecules in the second sample are polynucleotide molecules comprising polynucleotide sequences that are different from the nucleotide sequence of the polynucleotide molecules in the first sample.

B6

25. (Amended) The method of claim 20 wherein the polynucleotide probe is one of a plurality of polynucleotide probes comprising different nucleotide sequences.

Sub C3

27. (Amended) A method for evaluating binding properties of a polynucleotide probe comprising a predetermined nucleotide sequence to a target nucleotide sequence, said method comprising comparing the amount of hybridization of polynucleotides in a first sample to the polynucleotide probe with the amount of hybridization of polynucleotides in a second sample to the polynucleotide probe, wherein:

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(a) the first sample comprises a plurality of polynucleotide molecules comprising said target nucleotide sequence; and

(b) the second sample comprises a plurality of different polynucleotide molecules wherein each different polynucleotide molecule comprises a sequence that is different from the nucleotide sequences of any other polynucleotide molecules in said plurality of different polynucleotide molecules,

wherein the first sample is at least 75% pure in polynucleotide molecules comprising said target nucleotide sequence.

28. (Amended) The method of claim 27 wherein the predetermined nucleotide sequence of the polynucleotide probe is complementary to at least a hybridizable portion of the target nucleotide sequence in the first sample.

29. (Amended) The method of claim 27 wherein the target polynucleotide sequence in the first sample is a nucleotide sequence of a gene or gene transcript of a cell or organism, or

of an mRNA, cDNA or cRNA derived therefrom.

30. (Amended) The method of claim 27 wherein the plurality of different polynucleotide molecules in the second sample comprise nucleotide sequences of a plurality of genes or gene transcripts of a cell or organism.

33. (Amended) The method of claim 27 wherein the first sample is at least 90% pure in said polynucleotide molecules comprising said target nucleotide sequence.

34. (Amended) The method of claim 33 wherein the first sample is at least 95% pure in said polynucleotide molecules comprising said target nucleotide sequence.

35. (Amended) The method of claim 34 wherein in the first sample is at least 99% pure in said polynucleotide molecules comprising said target nucleotide sequence.

36. (Twice Amended) The method of claim 27 wherein each different polynucleotide molecule in the second sample does not comprise the target nucleotide sequence.

37. (Amended) The method of claim 36 wherein:

(a) the target polynucleotide sequence in the first sample is a sequence of a gene or gene transcript of a cell or organism; and

(b) the second sample comprises a polynucleotide sample from a deletion mutant of the cell or organism,

wherein the deletion mutant of the cell or organism does not express the gene or gene transcript.

38. (Amended) The method of claim 27 wherein the plurality of different polynucleotide molecules in the second sample comprises:

(a) polynucleotide molecules comprising the target nucleotide sequence, and

(b) a plurality of different polynucleotide molecules, each comprising a different nucleotide sequence and each not comprising the target nucleotide sequence.

39. (Twice Amended) The method of claim 38 wherein:

(a) the target nucleotide sequence comprises a sequence of a gene or gene transcript of a cell or organism; and

(b) the second sample comprises a polynucleotide sample from a wild-type strain of the cell or organism,

wherein the wild-type strain of the cell or organism expresses the gene or gene transcript.

40. (Amended) The method of claim 27 wherein:

(a) the first sample further comprises polynucleotide molecules that do not comprise the target nucleotide sequence; and

(b) the second sample lacks said polynucleotide molecules comprising said target nucleotide sequence.

42. (Amended) The method of claim 41 wherein:

(a) the target nucleotide sequence is a sequence of a gene or gene transcript of a cell or organism;

(b) the first sample comprises a polynucleotide sample from a wild-type strain of the cell or organism which expresses the gene or gene transcript; and

(c) the second sample comprises a polynucleotide sample from a deletion mutant of the cell or organism which does not express the gene or gene transcript.

43. (Amended) The method of claim 27 wherein

(a) the first sample further comprises polynucleotide molecules that do not comprise the target nucleotide sequence; and

(b) the second sample comprises:

(i) polynucleotide molecules comprising the target nucleotide sequence, and

(ii) a plurality of different polynucleotide molecules, each different polynucleotide molecule comprising a different nucleotide sequence and not comprising the target nucleotide sequence,

wherein the amount of polynucleotide molecules in the first sample comprising the target

nucleotide sequence differs by at least a factor of two from the amount of polynucleotide molecules in the second sample comprising the target nucleotide sequence.

55. (Amended) The method of claim 27 wherein a sensitivity of the polynucleotide probe is determined, wherein said sensitivity is the absolute amount of said polynucleotide molecules comprising said target nucleotide sequence that bind to said polynucleotide probe.

56. (Amended) The method of claim 55 wherein the sensitivity of the polynucleotide probe is determined from the amount of hybridization of said polynucleotide molecules in the first sample to the polynucleotide probe.

57. (Amended) The method of claim 27 wherein a specificity of the polynucleotide probe is determined, wherein said specificity is the amount of said polynucleotide molecules comprising said target nucleotide sequence that bind to said polynucleotide probe relative to the amount of polynucleotide molecules not comprising said target nucleotide sequence that bind to the probe under the same binding conditions.

58. (Amended) The method of claim 57 wherein the specificity of the polynucleotide probe is determined from a ratio of the amount of hybridization of polynucleotide molecules in the first sample to the polynucleotide probe to the amount of hybridization of polynucleotide molecules in the second sample to the polynucleotide probe.

59. (Amended) The method of claim 27 wherein the polynucleotide molecules in the first sample are detectably labeled.

62. (Amended) The method of claim 27 wherein:

(a) the polynucleotide molecules in the first sample are labeled with a first label; and

(b) the polynucleotide molecules in the second sample are labeled with a second label,

the first label being distinguishable from the second label.

67. (Amended) A method for evaluating binding properties of a plurality of polynucleotide probes to a target nucleotide sequence wherein each polynucleotide probe in the plurality of polynucleotide probes comprises a predetermined nucleotide sequence,

said method comprising comparing the amount of hybridization of polynucleotides in a first sample to each polynucleotide probe in the plurality of polynucleotide probes with the amount of hybridization of polynucleotides in a second sample to each polynucleotide probe in the plurality of polynucleotide probes, wherein:

(a) the first sample comprises a plurality of polynucleotide molecules comprising said target nucleotide sequence; and

(b) the second sample comprises a plurality of different polynucleotide molecules wherein each different polynucleotide molecule comprises a nucleotide sequence that is different from nucleotide sequence of any other polynucleotide molecules in said plurality of different polynucleotide molecules,

wherein the first sample is at least 75% pure in polynucleotide molecules comprising said target nucleotide sequence.

68. (Amended) The method of claim 67 wherein the predetermined nucleotide sequence of each polynucleotide probe is complementary to at least a hybridizable portion of the target nucleotide sequence.

69. (Amended) The method of claim 67 wherein a sensitivity of each polynucleotide probe in the plurality of different polynucleotide probes is determined, wherein said sensitivity is the absolute amount of said polynucleotide molecules comprising said target nucleotide sequence that bind to said polynucleotide probe.

70. (Amended) The method of claim 69 wherein the sensitivity of each polynucleotide probe in the plurality of polynucleotide probes is determined from the amount of hybridization of the polynucleotide molecules comprising said target nucleotide sequence in the first sample to each polynucleotide probe in the plurality of polynucleotide probes.

Sub C9

71. (Amended) The method of claim 67 wherein a specificity of each polynucleotide probe in the plurality of different polynucleotide probes is determined, wherein said specificity is the amount of said polynucleotide molecules comprising said target nucleotide sequence that bind to said polynucleotide probe relative to the amount of polynucleotide molecules not comprising said target nucleotide sequence that bind to the probe under the same binding conditions.

B16 cont

72. (Amended) The method of claim 71 wherein the specificity of each polynucleotide probe in the plurality of polynucleotide probes is determined from a ratio of

(a) the amount of hybridization of the polynucleotide molecules comprising said target nucleotide sequence in the first sample to each polynucleotide probe to

(b) the amount of hybridization of the plurality of different polynucleotide molecules in the second sample to each polynucleotide probe.

B17

75. (Amended) The method of claim 67 wherein the first sample comprises two or more different polynucleotide molecules

wherein none of the plurality of different polynucleotide molecules hybridizes or cross-hybridizes to a probe that also hybridizes or cross-hybridizes to another one of the plurality of different polynucleotide molecules.

B18

85. (Amended) The method of claim 84 wherein the second sample lacks polynucleotide molecules of said first sample.

REMARKS

The specification has been amended to delete page i which contains the Table of Contents. No new matter has been added. A marked version showing the amendment to the specification is attached hereto as Exhibit A.

Claims 1-75 and 81-85 were pending in the application. In the instant amendment, claims 2, 3, 31, 32 and 41 have been canceled without prejudice, and claims 1, 4-13, 15, 20, 22-23, 25, 27-30, 33-40, 42-47, 55-59, 62, 67-72, 75 and 85 have been amended to clarify the present invention. Upon entry of the above-made amendment, claims 1, 3-30, 33-40, 42-75

and 81-85 will be pending. A marked version of the amended claims showing changes made is attached hereto as Exhibit B. A clean version of the pending claims, as amended, is attached hereto as Exhibit C.

Claims 1, 27 and 67 have been amended to recite that the claimed methods are for evaluating *binding properties* of a probe to, e.g., a target molecule. Claims 1, 27 and 67 have also been amended to recite that the first sample is at least 75% pure in said target molecules (claim 1) or at least 75% pure in polynucleotide molecules comprising said target nucleotide sequence (claims 27 and 67). Support for the amendment is found in the specification at page 3, line 35 through page 4, line 3; page 8, lines 26-28; and page 9, lines 24-26.

Claims 8, 55 and 69 have been amended to recite that in the claimed methods, the sensitivity is the absolute amount of said target molecule that bind to said probe (claim 8) or the absolute amount of said polynucleotide molecules comprising said target nucleotide sequence that bind to said polynucleotide probe (claims 55 and 69). Support for the amendments is found in the specification at, e.g., page 39, line 35 through page 40, line 11. Claims 8, 55 and 69 have also been amended to recite in the first line of the claims that *a* sensitivity is determined.

Claims 10, 57 and 71 have been amended to recite that in the claimed methods, the specificity is the amount of said target molecules that bind to said probe relative to the amount of other molecules that bind the probe under the same binding conditions (claim 10) or the amount of said polynucleotide molecules comprising said target nucleotide sequence that bind to said polynucleotide probe relative to the amount of polynucleotide molecules not comprising said target nucleotide sequence to the probe under the same binding conditions (claims 57 and 71). Support for the amendments is found in the specification at, e.g., page 40, lines 12-29. Claims 10, 57 and 71 have also been amended to recite in the first line of the claims that *a* specificity is determined.

Claims 11, 58 and 72 have been amended to recite *"a* ratio" rather than "the ratio." Claim 4 has been amended to depend on claim 1 rather than the canceled claim 2, and claims 33 and 38 have been amended to depend on claim 27 rather than the canceled claim 31. Claims 1, 4-13, 15, 20, 22, 27-30, 33-40, 42-43, 55-59, 62, 67-72, 75 and 85 have also been amended such that the language of the claims is clearer.

No new matter has been added by these amendments. Entry of the foregoing

amendments and the following remarks are respectfully requested.

THE OBJECTIONS TO THE SPECIFICATION SHOULD BE WITHDRAWN

The disclosure is objected to because of the alleged informalities relating to the Table of Contents. Applicant has deleted the Table of Contents, thereby obviating the objection. Applicant respectfully submit that the objection to the specification should be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 112, SECOND PARAGRAPH SHOULD BE WITHDRAWN

Claims 1-75 and 81-85 are rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In paragraph 4a of the Office Action, claims 1-75 and 81-85 are rejected as allegedly being indefinite as being incomplete for omitting essential steps. The Examiner contends that the omitted steps are the method steps for comparing the amount of binding to thereby evaluate binding of probe to target, such as steps of labeling, hybridizing, detecting, measuring and comparing. Applicant respectfully submits that the essential step of the claimed methods is the step of comparing which is recited in the claims. The other steps are not essential steps of the claimed methods in that the claimed methods are directed to methods of evaluating *binding properties* of a probe to a target molecule by comparing the difference in the amount of binding of the target molecule and the amount of binding of, e.g., other molecules different from the target molecule, to the probe. The methods of the invention are not limited to any particular way of obtaining the amounts of binding. For example, the methods are equally applicable to amounts of binding measured in a hybridization experiment which involves the steps of labeling, hybridizing, detecting, measuring as well as to amounts of binding saved in a database. Thus, Applicant respectfully submits that the claims do not contain gaps, and that the rejection is in error and should be withdrawn.

In paragraphs 4b and 4r of the Office Action, claims 2-6 and 31-35[1] are rejected as

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[1] In the Office Action, claim 36 is also included in this group of claims and (continued...)

allegedly being indefinite for the recitations "substantially pure sample" and "pure." Applicant has canceled claims 2, 3, 31 and 32 and amended claims 4-6 and 33-35 to recite that the first sample is at least 75%, 90% or 99% pure in the target molecule or the polynucleotide molecule comprising said target nucleotide sequence. The rejections are therefore obviated and should be withdrawn.

In paragraphs 4c, 4u, and 4cc, claims 8-9, 55-56, and 69-70 are rejected as allegedly being indefinite in claims 8, 55, and 69, respectively, for the recitation "the sensitivity of the probe" because probe "sensitivity" lacks proper antecedent basis in claims 1, 27, and 67, respectively. Applicant has amended claims 8, 55, and 69 to recite "a sensitivity" in accordance with the Examiner's suggestion. The rejection is therefore obviated and should be withdrawn.

In paragraphs 4d, 4v, and 4dd, claims 8-9, 55-56, and 69-70 are also rejected as allegedly being indefinite in claims 8, 55, and 69, respectively, for the recitation "sensitivity of the probe" because "sensitivity" allegedly is a non-specific qualitative term which requires definition or criteria for determining. Applicant has amended claims 8, 55, and 69 to include a definition for sensitivity. The rejection is therefore obviated and should be withdrawn.

In paragraphs 4e, 4w, and 4ee, claims 8-9, 55-56, and 69-70 are further rejected as allegedly being indefinite in claims 8, 55, and 69, respectively, for the recitation "sensitivity of the probe" because allegedly essential steps for determining "sensitivity" are omitted, such omission amounting to a gap between the steps. The Examiner contends that the omitted steps are the method steps such as, hybridizing, measuring and determining. Applicant respectfully submits that what is essential to the methods of claims 8-9, 55-56, and 69-70 is that the absolute amount of binding of the target molecules to the probe is determined. The other steps are not essential steps of these claimed methods since these methods recite that the sensitivity of a probe in binding to a target molecule is determined, wherein the sensitivity is the absolute amount of binding of the target molecule to the probe. The methods of the invention are not limited to any particular way of obtaining the amounts of binding. For example, the methods are equally applicable to amounts of binding measured in a

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[1] (...continued)
rejected for the recitations "substantially pure sample" and "pure." However, since claim 36 does not recite "substantially pure sample" or "pure," Applicant believes that it was included in this group by error.

hybridization experiment which involves the steps of hybridizing, measuring and determining as well as to amounts of binding saved in a database. Thus, Applicant respectfully submits that the claims do not contain gaps, and that the rejection is in error and should be withdrawn.

In paragraphs 4f, 4x, and 4ff, claims 10-11, 57-58 and 71-72 are rejected as allegedly being indefinite in claims 10, 57, and 71, respectively, for the recitation "the specificity of the probe" because probe "specificity" lacks proper antecedent basis in claims 1, 27, and 67, respectively. Applicant has amended the claims 10, 57, and 71 to recite "a specificity" in accordance with the Examiner's suggestion. The rejection is therefore obviated and should be withdrawn.

In paragraphs 4g, 4y, and 4gg, claims 10-11, 57-58 and 71-72 are also rejected as allegedly being indefinite in claims 10, 57, and 71, respectively, for the recitation "specificity of the probe" because "specificity" is a non-specific qualitative term which requires definition or criteria for determining. Applicant has amended claims 10, 57 and 71 to include a definition for specificity. The rejection is therefore obviated and should be withdrawn.

In paragraphs 4h, 4z, and 4hh, claims 10-11, 57-58 and 71-72 are further rejected as allegedly being indefinite in claims 10, 57, and 71, respectively, for the recitation "specificity of the probe" because essential steps for determining "specificity" are omitted. The Examiner contends that the omitted steps are the method steps such as, hybridizing, measuring, comparing and determining. Applicant respectfully submits what is essential to the methods of claims 10-11, 57-58 and 71-72 is that the amount of the target molecules that bind to the probe relative to the amount of other molecules that bind the probe under the same binding conditions is determined. The other steps are not essential steps of the methods of these claims since the claims recite that the amount of the target molecules that bind to the probe relative to the amount of other molecules that bind the probe under the same binding conditions is determined. The methods of the invention are not limited to any particular way of obtaining the amounts of binding. For example, the methods are equally applicable to amounts of binding measured in a hybridization experiment which involves the steps of hybridizing, measuring and determining as well as to amounts of binding saved in a database. Thus, Applicant respectfully submits that the claims do not contain gaps, and that the rejection is in error and should be withdrawn.

In paragraphs 4i, 4aa, and 4ii, claims 11, 58 and 72 are rejected as allegedly being

indefinite for the recitation "the specificity of the probe is determined from the ratio of the amount of binding... to the probe" because "ratio" lacks proper antecedent basis in the basis claims. Applicant has amended the claims to recite "a ratio" in accordance with the Examiner's suggestion. The rejection is therefore obviated and should be withdrawn.

In paragraph 4j, claim 11 is rejected as allegedly being indefinite for the recitation "the specificity of the probe is determined from the ratio of the amount of binding...to the probe" because essential steps for providing "the ratio" are omitted. The Examiner contends that the omitted steps are the method steps such as, measuring, comparing and determining. Applicant respectfully submits that what is essential to claim 11 is that the amount of the target molecules that bind to the probe relative to the amount of other molecules that bind the probe under the same binding conditions is determined. The other steps mentioned by the Examiner are not essential steps of the claimed methods since claim 11 recites that the amount of the target molecules that bind to the probe relative to the amount of other molecules that bind the probe under the same binding conditions is determined by use of a ratio of the amount of the target molecules that bind to the probe relative to the amount of other molecules that bind the probe. The methods of the invention are not limited to any particular way of obtaining the amounts of binding. For example, the methods are equally applicable to amounts of binding measured in a hybridization experiment which involves the steps of hybridizing, measuring and determining as well as to amounts of binding saved in a database. Thus, Applicant respectfully submits that the claims do not contain gaps, and that the rejection is in error and should be withdrawn.

In paragraph 4k, claims 20-26 are rejected as allegedly being indefinite in claim 20 for the recitation "probe having a particular nucleotide sequence" because of the word "particular." Applicant has amended claim 20 to replace the word "particular" with the word "predetermined." Applicant respectfully submits that the rejection is thus obviated and should be withdrawn. In paragraphs 4l and 4bb, claims 27-66, 67-75, and 84 are similarly rejected. Applicant has also amended claims 27 and 67 similarly. The rejection of these claims is therefore also obviated and should be withdrawn.

In paragraph 4m, claims 27-66 and 84 are rejected as allegedly being indefinite in claim 27, step (b) for the recitation "a plurality of different polynucleotide molecules" because "polynucleotide molecules" lacks proper antecedent basis in step (a) which recites

"target polynucleotide" and target nucleotide sequence." Applicant respectfully points out that step (b) limits the second sample, which is independent of the first sample. Applicant has also amended claim 27 to clarify that the second sample comprises a plurality of different polynucleotide molecules *wherein each different polynucleotide molecule comprises a sequence that is different from the nucleotide sequences of any other polynucleotide molecules in said plurality of different polynucleotide molecules* (emphasis added). The rejection should therefore be withdrawn.

In paragraph 4n, claims 27-66 and 84 are rejected as allegedly being indefinite in Claim 27, step (b) for the recitation "a plurality of different polynucleotide molecules" because "different" is a relational term but it is unclear what relationship is being described. Applicant has amended claim 27, step (b) to recite that the second sample comprises a plurality of different polynucleotide molecules wherein *each different polynucleotide molecule comprises a sequence that is different from the nucleotide sequences of any other polynucleotide molecules in said plurality of different polynucleotide molecules* (emphasis added). The rejection is therefore obviated and should be withdrawn. In paragraphs 4p claim 30 is similarly rejected for the use of "different." Applicant has amended claim 30 similarly so that the rejection is also obviated and should be withdrawn.

In paragraph 4o, claim 29 is rejected as allegedly being indefinite for the word "corresponds" in the recitation "wherein the target polynucleotide in the first sample corresponds to a gene or gene transcript." Applicant has amended the claim to recite that the target nucleotide sequence in the first sample *is* a nucleotide sequence of a gene or gene transcript of a cell or organism. The rejection is therefore obviated and should be withdrawn. In paragraphs 4p and 4s, claims 30, 37, 39 and 42 are similarly rejected for the use of the word "corresponds" or the term "corresponding to." Applicant has amended these claims similarly so that these rejections are also obviated and should be withdrawn.

In paragraph 4t, claims 40 and 43 are rejected as allegedly being indefinite for the recitation "the first sample further comprises polynucleotide molecules having a nucleotide sequence different from the target nucleotide sequence of said same target polynucleotide." Applicant has amended the claims to clarify that the first sample further comprises polynucleotide molecules *not comprising the target nucleotide sequence* (emphasis added). The rejection is therefore obviated and should be withdrawn.

THE REJECTION UNDER 35 U.S.C. § 102
SHOULD BE WITHDRAWN

Claims 1-36, 38-41, 43-45, 48-75 and 81-85 are rejected under 35 U.S.C. § 102(b) as being anticipated by Brown et al., U.S. Patent No. 5,807,522 ("Brown"). Applicants respectfully disagree with the Examiner for the reasons presented below.

A claim is anticipated under 35 U.S.C. § 102 only if each and every element and limitation as set forth in the claim is found, either expressly described or inherently present, in a single prior art reference. *Glaxo, Inc. v. Novopharm Ltd.*, 52. F.3d 1043, 1047 (Fed. Cir. 1995). There must be *no differences* between the claimed invention and the reference disclosure as viewed by a person of ordinary skill in the field of the invention. *Scripps Clinic & Research Fdn. v. Genentech, Inc.* 927 F. 2d. 1565, 1576 (Fed. Cir. 1991).

The present invention teaches methods of evaluating binding properties of the binding of a probe to its target molecules. As described in the specification, such binding properties include sensitivity and specificity (see, e.g., specification at page 3, line 35 through page 4, line 3). The claimed methods involve comparing the amount of binding of target molecules to a probe with the amount of binding of other molecules to the probe so as to evaluate, e.g., the sensitivity and specificity of the probe. For example in claim 27, binding properties of a polynucleotide probe comprising a predetermined nucleotide sequence to a target nucleotide sequence is determined by a method comprising comparing the amount of hybridization of polynucleotides in a first sample to the polynucleotide probe with the amount of hybridization of polynucleotides in a second sample to the polynucleotide probe, wherein the first sample is at least 75% pure in polynucleotide molecules comprising the target nucleotide sequence, whereas the second sample comprises a plurality of different polynucleotide molecules, each comprising a sequence that is different from the nucleotide sequences of any other polynucleotide molecules in the plurality of different polynucleotide molecules.

Brown teaches a method and apparatus for forming microarrays of biological samples on a support. Brown also teaches hybridization of nucleic acid samples to the microarray. For example, in its example 1, Brown teaches hybridization to its microarray of two pools of nucleic acids, in which one pool contains random amplification products of the 6 large yeast chromosomes and the other pool contains random amplification products of the 10 small yeast chromosomes. The hybridization values of spots or clones on the array identify to

which of the two pools the clones belong and correlate the clone to the location on the yeast genome. Therefore, Brown merely teaches determining the binding of molecules in samples containing pools of random amplification products of more than one chromosomes to its probes.

With respect to claims 1, 27 and 67, the Examiner contends that "Brown et al. disclose methods for evaluating binding of a plurality of polynucleotide probes to a target polynucleotide wherein each probe has a particular nucleotide sequence, said method comprising comparing the amount of hybridization in a first sample to the amount of hybridization in a second sample and wherein the first sample comprises a plurality of the same target polynucleotides (i.e. amplified copies of fragments from the large chromosomes) and the second sample comprises a plurality of different polynucleotide molecules wherein the different polynucleotide molecules have a different nucleotide sequence (i.e. the second sample comprises amplified copies of fragments from the small chromosomes) (Example 1, Column 16, line 39-56)." Applicant respectfully point out that the sample containing amplified molecules from the 6 large chromosomes is not a sample which contains mostly the target molecule as required by the amended claims of the present invention. As discussed above, in claims 1, 27, and 67 of the present invention, the first sample is at least 75% pure in the target molecule. In contrast, in Brown both samples comprise pools of random amplification products of more than one chromosome. Nowhere does Brown teach a sample which is at least 75% pure in molecules that are target molecules of a probe. Nor does Brown teach a method of evaluating binding properties of a probe to its target molecule by comparing the binding of the probe to such a sample with the binding of the probe to a sample which contains various different molecules, e.g., molecules other than the target molecule.

With respect to claims 2-7 and 31-35, the Examiner contends that Brown discloses methods wherein the first sample is "substantially pure" in the same target, i.e. the chromosomes are gel-extracted and amplified (Column 16, lines 39-47), because the gel extractions and amplification of Brown are allegedly reasonably interpreted as "substantially pure" and/or "99%" pure because the mRNA of Brown et al. is at least substantially purified and/or 99% purified from the cell. Applicant respectfully submits that, as discussed above, Brown's sample is not a sample which is at least 75% pure in a target molecule of a probe as

specified by amended claims 1 and 27.

With respect to claims 8, 55 and 69, the Examiner contends that Brown discloses the method wherein the sensitivity of the probe is determined (Column 16, line 66-Column 17, line 8), because Brown determines amount of binding which, according to the specification, determines sensitivity (Column 16, line 66 to Column 17, line 8). With respect to claims 9, 56 and 70, the Examiner contends that Brown discloses the method wherein the sensitivity is determined from the amount of binding to the target in the first sample to the probe (Column 16, line 66 to Column 17, line 8). Applicant respectfully points out that the section in Brown as cited by the Examiner teaches the correlation of hybridization value of each clone on the array to the physical map position of yeast chromosomes to generate a color karyotype of the yeast genome. Nowhere does Brown teach a *sensitivity of the probe that is the absolute amount of said target molecules that bind to said probe*. Nowhere does Brown teach a sample which is at least 75% pure in a target molecule. Nor does Brown teach a method of evaluating binding properties of a probe to its target molecule by comparing the binding of the probe to such a sample with the binding of the probe to a sample which contains various different molecules, e.g., molecules other than the target molecules.

With respect to claim 10, 57 and 71, the Examiner contends that Brown discloses a method wherein the specificity of the probe is determined (Column 17, lines 9-17), because Brown determines the amount of hybridization vs. non-specific hybridization by determining the amount of chromosome-specific vs. non-specific binding (Column 17, lines 9-17). With respect to claim 11, 58 and 72, the Examiner contends that Brown discloses a method wherein the specificity is determined by the ratio of specific to non-specific binding (Column 17, lines 9-17). Applicant respectfully points out that the section in Brown as cited by the Examiner teaches that red signals identify a clone from one of the 6 small chromosomes whereas a green signal identify a clone from one of the ten large chromosomes, and that confirmation of specific hybridization to a probe is achieved by comparison of hybridization to control probes by the same sample. Nowhere does Brown teach a *specificity that is the amount of said target molecules that bind to said probe relative to the amount or level of other molecules that bind the probe under the same binding conditions*. Nor does Brown teach a method of evaluating binding properties of a probe to its target molecule by comparing the binding of the probe to such a sample with the binding of the probe to a

sample which contains various different molecules, e.g., molecules other than the target molecules. Nowhere does Brown teach a sample which is at least 75% pure in a target molecule.

Other dependent claims (claims 9, 11-26, 28-30, 36, 38-41, 43-45, 48-54, 56, 58-66, 68, 70, 72-75, and 81-85) are rejected based on additional recitations in these claims. Applicant respectfully submits that since Brown does not teach the independent claims upon which these claims depend, these dependent claims are not anticipated. These rejections should also be withdrawn. Therefore, Applicants respectfully submits that the rejections of claims 1-36, 38-41, 43-45, 48-75 and 81-85 under 37 C.F.R. § 102(b) based on Brown should be withdrawn.

THE REJECTIONS UNDER 35 U.S.C. § 103(a) SHOULD BE WITHDRAWN

Claims 37 and 42 are rejected under 35 U.S.C. § 103(a) as being obvious over Brown et al., U.S. Patent No. 5,807,522 ("Brown"). Claims 46-47 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Brown in view of Schena et al., 1995, Science 270:467-470 ("Schena"). Applicants respectfully disagree with the Examiner for the reasons presented below.

A finding of obviousness under 35 U.S.C. § 103(a) requires a determination that the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious to one of ordinary skill in the art at the time the invention was made. *Graham v. Deere*, 383, U.S. 1 (1956). The relevant inquiry is whether the prior art suggests the invention and whether the prior art provides one of ordinary skill in the art with a reasonable expectation of success. Both the suggestion and the reasonable expectation of success must be found in the prior art. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991).

As discussed above, the present invention teaches methods of evaluating binding properties of a probe to its target molecules. As described in the specification, such binding properties include sensitivity and specificity (see, e.g., specification at page 3, line 35 through page 4, line 3). The claimed methods involve comparing the amount of binding of target molecules to a probe with the amount of binding of other molecules to the probe so as to evaluate, e.g., the sensitivity and specificity of the probe. For example, in claim 27, binding

properties of a polynucleotide probe comprising a predetermined nucleotide sequence to a target nucleotide sequence is determined by a method comprising comparing the amount of hybridization of polynucleotides in a first sample to the polynucleotide probe with the amount of hybridization of polynucleotides in a second sample to the polynucleotide probe, wherein the first sample is at least 75% pure in polynucleotide molecules comprising the target nucleotide sequence, whereas the second sample comprises a plurality of different polynucleotide molecules, each comprising a sequence that is different from the nucleotide sequences of any other polynucleotide molecules in the plurality of different polynucleotide molecules. Brown teaches method and apparatus for forming microarrays of biological samples on a support. Brown also teaches hybridization of nucleic acid samples to the microarray. For example, in its example 1, Brown teaches hybridization of two pools of nucleic acids, one contains random amplification products of the 6 large yeast chromosomes and the other contains random amplification products of the 10 small yeast chromosomes, to its microarray. The hybridization values of spots or clones on the array identify which of the two pools the clones belong to and correlate them to the location on the yeast genome. Therefore, Brown merely teaches of determining the binding of molecules in samples containing pools of random amplification products of more than one chromosomes to its probes.

With respect to claim 37, the Examiner contends that "it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the samples of Brown et al. to analyze samples wherein the second sample comprises a deletion mutant as they suggest to thereby rapidly evaluate probe-target binding for the expected benefit of rapid and convenient detection of mutant-specific disease state as taught by Brown et al." With respect to claim 42, the Examiner contends that "it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the samples of Brown et al. to analyze samples wherein the second sample comprises a deletion mutant as they suggest to thereby rapidly evaluate probe-target binding for the expected benefit of rapid and convenient detection of mutant-specific disease state as taught by Brown." Applicant respectfully point out that Brown does not teach a method of evaluating binding properties of a probe to its target molecule by comparing the binding to the probe using a sample which is at least 75% pure in the target molecule of the probe with the binding

to the probe using a sample which contains molecules, e.g., molecules other than the target molecules. An ordinary skilled person in the art would not be motivated by Brown to a method for evaluating the binding properties of a probe. Nor would an ordinary skilled person in the art be motivated by Brown to evaluate binding properties of a probe to its target molecule by comparing the binding to the probe using a sample which is at least 75% pure in the target molecule of the probe with the binding to the probe using a sample which contains molecules, e.g., molecules other than the target molecules. Brown does not provide an ordinary skilled person in the art a reasonable expectation of success of such methods. Thus, Applicant respectfully submits that the rejections under 35 U.S.C. § 103(a) over Brown should be withdrawn.

Claims 46-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Brown and further in view of Schena et al., 1995, Science 270:467-470 ("Schena"). The Examiner contends that "it would have been obvious to one of ordinary skill in the art at the time the claimed invention was made to modify the differing amount of polynucleotides in the samples of Brown et al. to differ by at least a factor of 100 as taught by Schena et al. and to quantitatively measure complex gene expression patterns to thereby characterize physiological and pathological conditions for the expected benefit of linking gene expression to clinical diagnosis as taught by Schena et al." As discussed above, an ordinary skilled person in the art would not be motivated by Brown to a method for evaluating the binding properties of a probe. Nor does an ordinary skilled person in the art would be motivated by Brown to a method of evaluating binding properties of a probe to its target molecule by comparing the binding to the probe using a sample which is at least 75% pure in the target molecule of the probe with the binding to the probe using a sample which contains molecules, e.g., molecules other than the target molecules. Brown does not provide an ordinary skilled person in the art a reasonable expectation of success of such methods. Schena teaches monitoring gene expression patterns with a cDNA microarray. In Schena, a sample containing fluorescent molecules prepared from total *Arabidopsis* mRNA of the wild-type and a transgenic cell line overexpressing HAT4 are used to hybridize to the microarray. Schena does not teach or suggest a method for evaluating the binding properties of a probe. Nor does Schena teach or suggest a method of evaluating binding properties of a probe to its target molecule by comparing the binding to the probe using a sample which is at least 75%

pure in the target molecule of the probe with the binding to the probe using a sample which contains molecules, e.g., molecules other than the target molecules. Therefore, Schena does not add what are missing in Brown. Thus, Applicant respectfully submits that the rejections under 35 U.S.C. § 103(a) over Brown in view of Schena should be withdrawn.

CONCLUSION

Applicants respectfully request entry of the foregoing amendments and remarks into the file of the above-identified application. Applicants believe that each ground for rejection has been successfully overcome or obviated, and that all the pending claims are in condition for allowance. Withdrawal of the Examiner's rejections and allowance of the application are respectfully requested.

Respectfully submitted,

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Enclosures